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THERMOSPRAY LIQUID CHROMATOGRAPHY/MASS SPECTROMETRY OF MUSTARD AND ITS METABOLITES

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Recently, considerable interest has been evinced in detecting and analyzing chemical agents. Though gas chromatography is commonly used to analyze them, mass spectral data is required to positively confirm their presence. Because thermospray provides soft ionization and interesting fragmentation patterns under discharge conditions, the thermospray behavior of bis(2-chloroethyl)sulfide and its metabolites has been investigated. All of the metabolites except mustard sulfone and thiodiglycol sulfone indicate the presence of a three-membered cyclic sulfonium ion intermediate or its equivalent. In the case of mustard, the most abundant ion is this charged cyclic structure or its equivalent. It formed one of the prominent ions in other analytes. In the aqueous hydrolysis of bis(2-chloroethyl)sulfide, the presence of this type of cyclic sulfonium intermediate has often been postulated and invoked. Other thermospray reactions observed include polymerizations and nucleophilic substitutions.

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PREFACE

The work described in this report was authorized under Project No. 1-32-85-000-A-372. This work was started in March 1986 and completed in November 1986.

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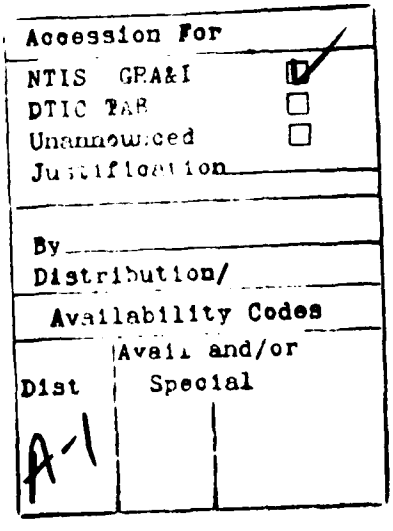

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THERMOSPRAY LIQUID CHROMATOGRAPHY/MASS SPECTROMETRY OF MUSTARD AND ITS METABOLITES

1. INTRODUCTION

In light of its recently alleged use as a warfare agent in the Middle East armed conflict, mustard gas has attracted considerable attention. As a consequence, procedures for separating, detecting, and quantitating trace amounts of mustard and its metabolites present in the biological media are urgently needed. Analysis of bis(2-chloroethyl)sulfide (1), known as mustard or mustard gas, has always been difficult due to the reactive nature of the molecule and its high toxicity. The ability to analyze for the presence of mustard and its metabolites or degradation products from the physiological matrices is of considerable importance in detecting and identifying them as well as in understanding the mechanism of their biological behavior. Coupled to this is the need to develop proper decontamination procedures and the treatment of the physiological manifestations resulting from exposure to the highly toxic chemical agent, namely mustard.

Although it has not been used as a chemotherapeutic agent, mustard's usefulness against some viruses has been reported, and alkylating moieties similar to mustard have been incorporated into many therapeutic agents. Bohme et al suggest that alkylation by mustard occurs in stepwise fashion.[1,2] Intramolecular attack of the sulfur on the beta carbon concurrently with the loss of chlorine results in the formation of the cyclic sulfonium intermediate (2) or its equivalent, which is then available for nucleophilic substitution reactions. The existence of such a cyclic sulfonium intermediate has often been invoked to rationalize the products formed during its hydrolysis.[3,4] Cell death or mutation occurs when in vivo nucleophilic attack takes place. However, in the presence of water, it forms a thiirane intermediate that is capable of yielding half-mustard (mustard chlorohydrin) (3) and repetition of the above sequence will result in thiodiglycol (4) one of the major products of mustard metabolism.[5] Mustard also undergoes in vivo oxidation to mustard sulfoxide (5) and mustard sulfone (6).[6] The former has been reported to be almost completely harmless, whereas the latter is said to be as toxic as the parent compound.[7] It must, however, be stated that these reports need further substantiation. The biological oxidation products of thiodiglycol (3), namely, the sulfoxide (7) and the sulfone (8), have also been isolated from the metabolism of mustard and its oxidative decontamination.[7]

Gas chromatography (GC) has been the method of choice for quantifying mustard, and mass spectrometry (MS) is used for confirmation.[8] In the past, high-performance liquid chromatography (HPLC) lacked a detector that would allow it to be used for mustard analysis. This problem has been partially overcome by incorporating chromogenic moieties and by other detector modifications.[9,10] The thermospray (TSP) interface for liquid chromatography/mass spectrometry (LC/MS) has provided a means to gain mass spectral data on compounds from the effluent of an HPLC. Thermospray LC/MS frequently furnishes useful information and exhibits lower detection levels than HPLC/MS techniques.[11] Thermospray using ammonium acetate as an ionizing adjunct has been characterized as a soft ionization technique producing spectra similar to ammonia-induced chemical ionization (CI) and fast atom bombardment. An auxiliary discharge electrode in the TSP source permits the use of non-aqueous solvents and thus alleviates the need to use ammonium salts as ionization adjuncts.[11] In addition, the discharge mode produces an increase in fragmentation, which proves to be of considerable help in elucidating structures of organic compounds. Fragmentation in TSP is a complex mixture of condensed and gas-phase reactions, reflecting

the characteristic chemistry of the compounds under investigation.[13] Thus, in the TSP MS analysis at temperatures greater than necessary for the vaporization, molecular decomposition produced ions consistent with the condensed-phase chemistry of the substrate, and accordingly, the mechanism for the condensed-phase reaction has been deduced.[14] Bursey and co-workers[15] and Alexander and Kebale[16] conclusively demonstrate that the ionization of neutral analytes is due to gas-phase ionization processes. The ions observed in the TSP LC/MS can arise from condensed- and gas-phase reactions. The objective of this report is to illustrate the unique capabilities of TSP LC/MS in analyzing mustard and its metabolites. Six oxidation and hydrolysis metabolites of mustard have been studied.

2. EXPERIMENTAL SECTION

The mustard was provided by the U.S. Army Medical Research Institute of Chemical Defense (Aberdeen Proving Ground, MD) and was diluted with methanol to a concentration of 0.005M. Using known methods,[17-19] mustard sulfone (6), mustard sulfoxide (5), half mustard (3), thiodiglycol sulfone (8), and thiodiglycol sulfoxide (7) were synthesized from either mustard or thiodiglycol, and their identity and purity were confirmed by GC/MS and NMR. Thiodiglycol (4) was procured from Aldrich Chemical Company, Incorporated (Milwaukee, WI). All analytes were first dissolved in anhydrous methanol and directly injected into the TSP source using the discharge mode. Characteristic positive and negative ion mass spectra were recorded for all of the compounds listed above except for the negative ion spectrum of mustard. The negative ion mass spectra of half-mustard and thiodiglycol (Figures 1 and 2) are given as examples. Analytes other than mustard were analyzed at a concentration of 0.01M in methanol. Methanol was glass distilled from EM Science (Cherry Hill, NJ) and filtered through a 0.45-μm membrane [Millipore, Incorporated, (Bedford, MA)] before being used for TSP LC/MS.

All studies were accomplished on a Finnigan 4500 MS Modified with a Vestec interface and used the INCOS data system for the MS control. A Waters model 510 LC pump was used with a pulse dampener, model LP21 LoPulse, from Scientific Systems, Incorporated, and a Rheodyne injector model 7125. The conditions were as follows: LC flow rate = 1.2 mL/min, mobile phase = 100% methanol, injection volume = 20 μL. Thermospray control temperature = 100 °C, TSP tip temperature = 150 °C, TSP source temperature = 300 °C, and the TSP used the discharge electrode with all injections.

3. RESULTS AND DISCUSSION

Although the molecular ion peak for mustard was observed, the base peak on electron impact (EI) was the result of the - cleavage with a loss of α –CH_2Cl from the molecular ion, and the second most prominent was the peak at m/z = 63 due to the loss of -[CH_2CH_2Cl] ion.[20] However according to these authors, the most intense peak of the methane and isobutane-induced positive CI of the mustard is the m/z = 123 ion. In addition, these authors claim that the positive CI is more sensitive than the negative CI. They also observed the $[M+H]^+$ ion.

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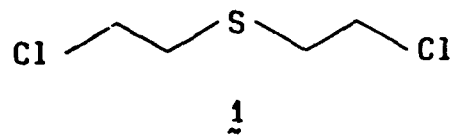

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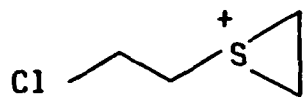

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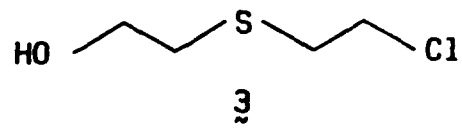

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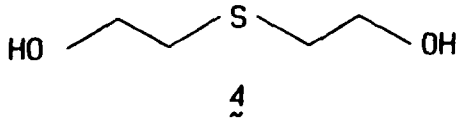

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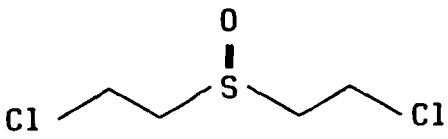

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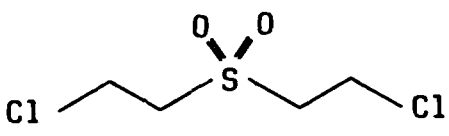

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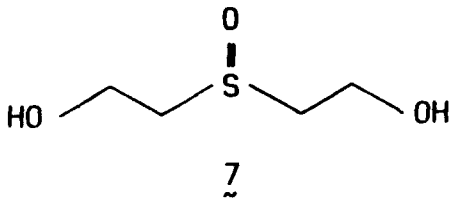

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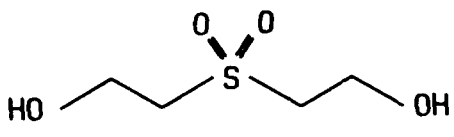

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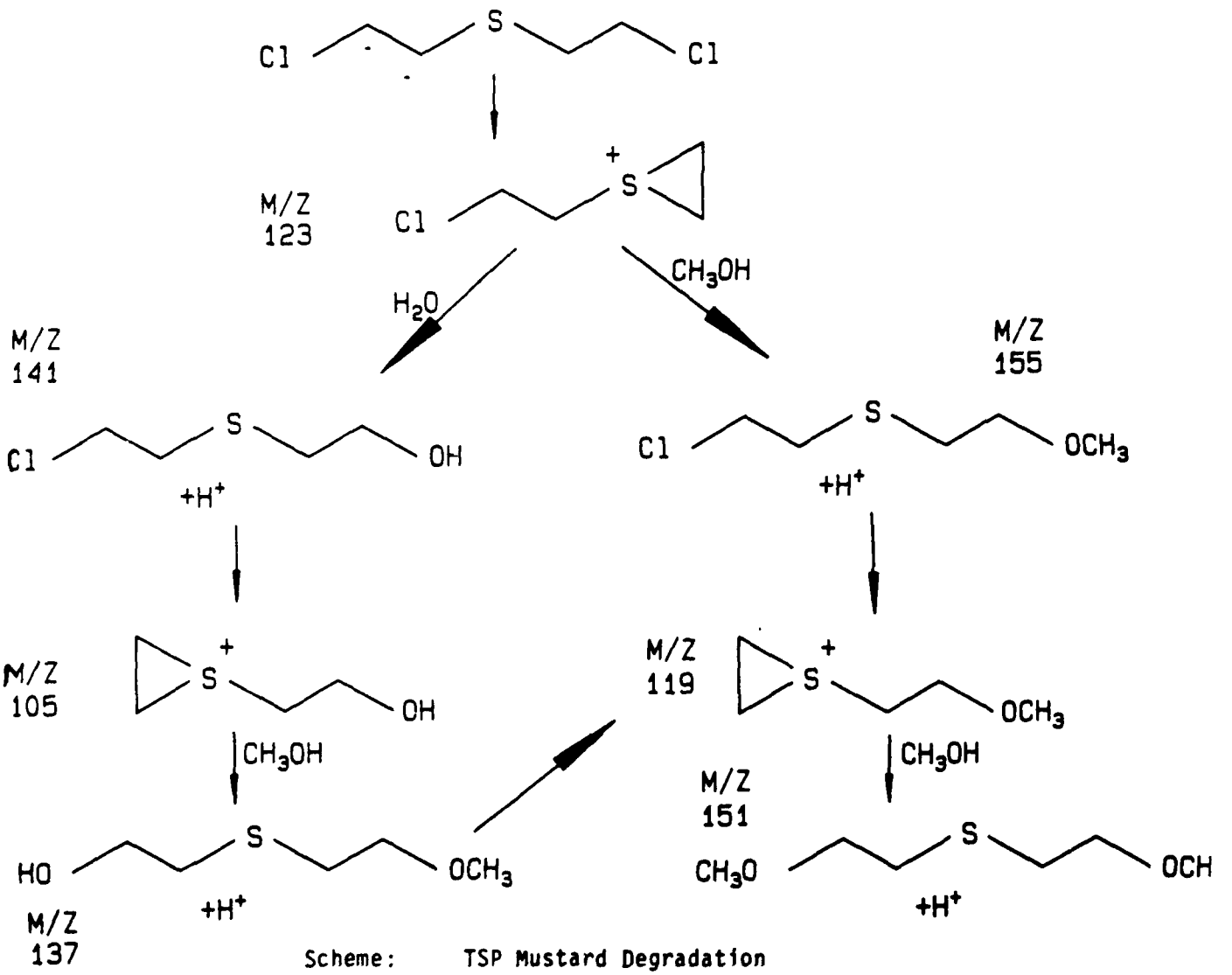
STRUCTURES



Scheme: TSP Mustard Degradation

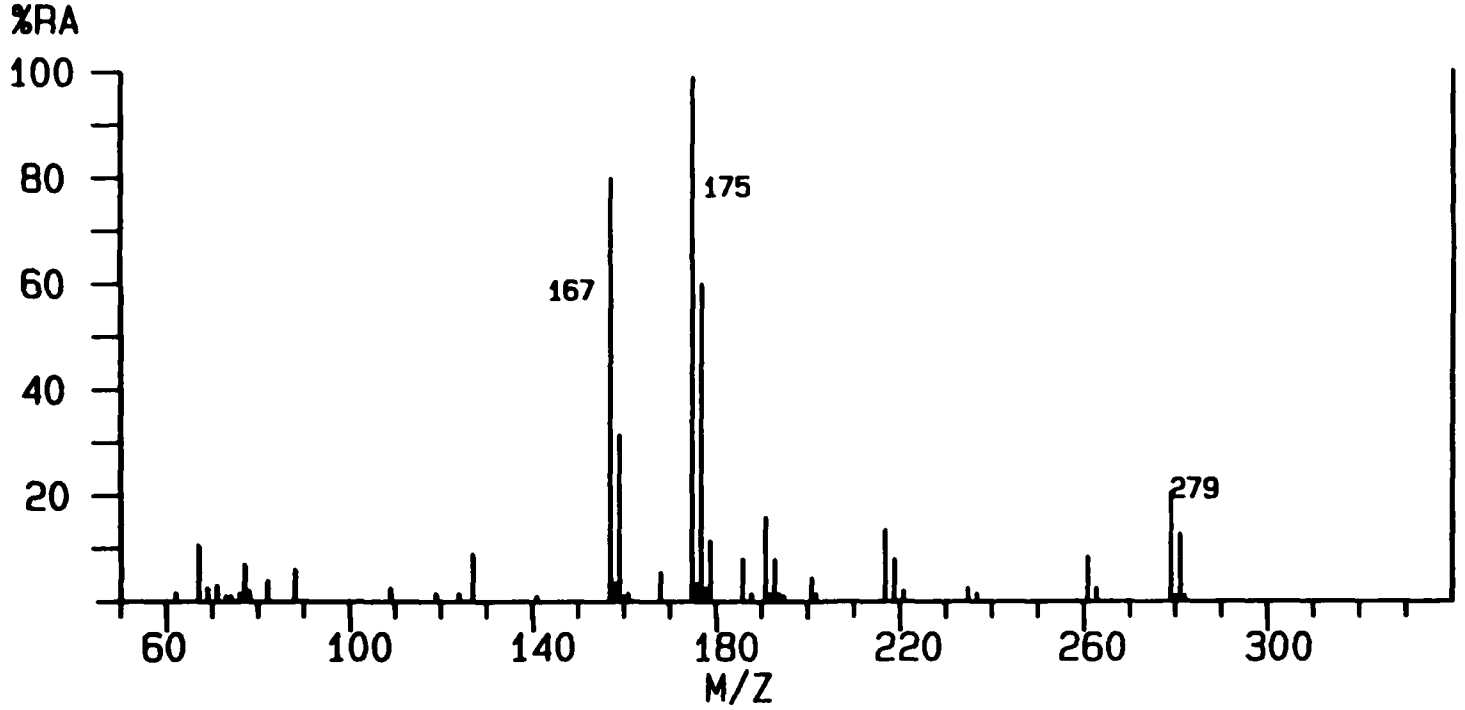


Figure 1. TSP Negative Ion Spectrum of Half-Mustard (3).

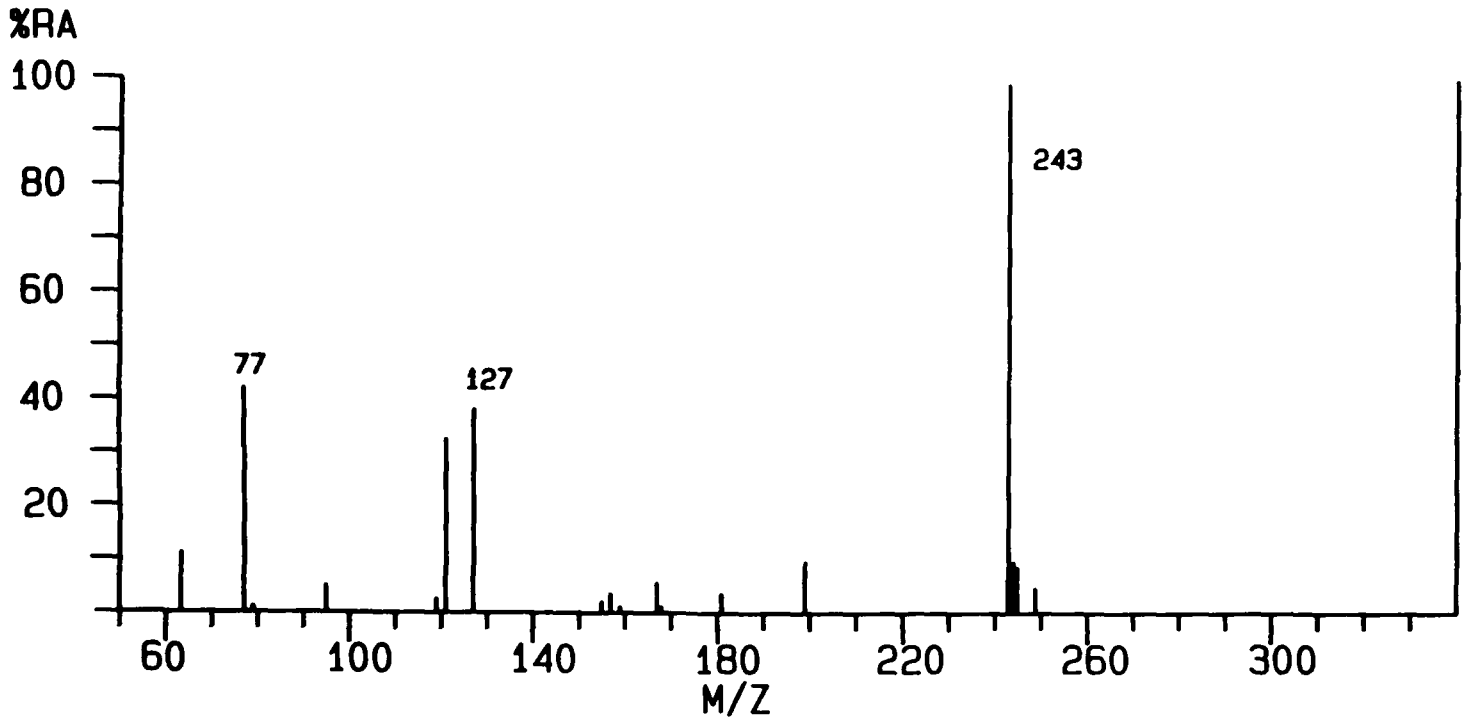


Figure 2. TSP Negative Ion Spectrum of Thiodiglycol (4).

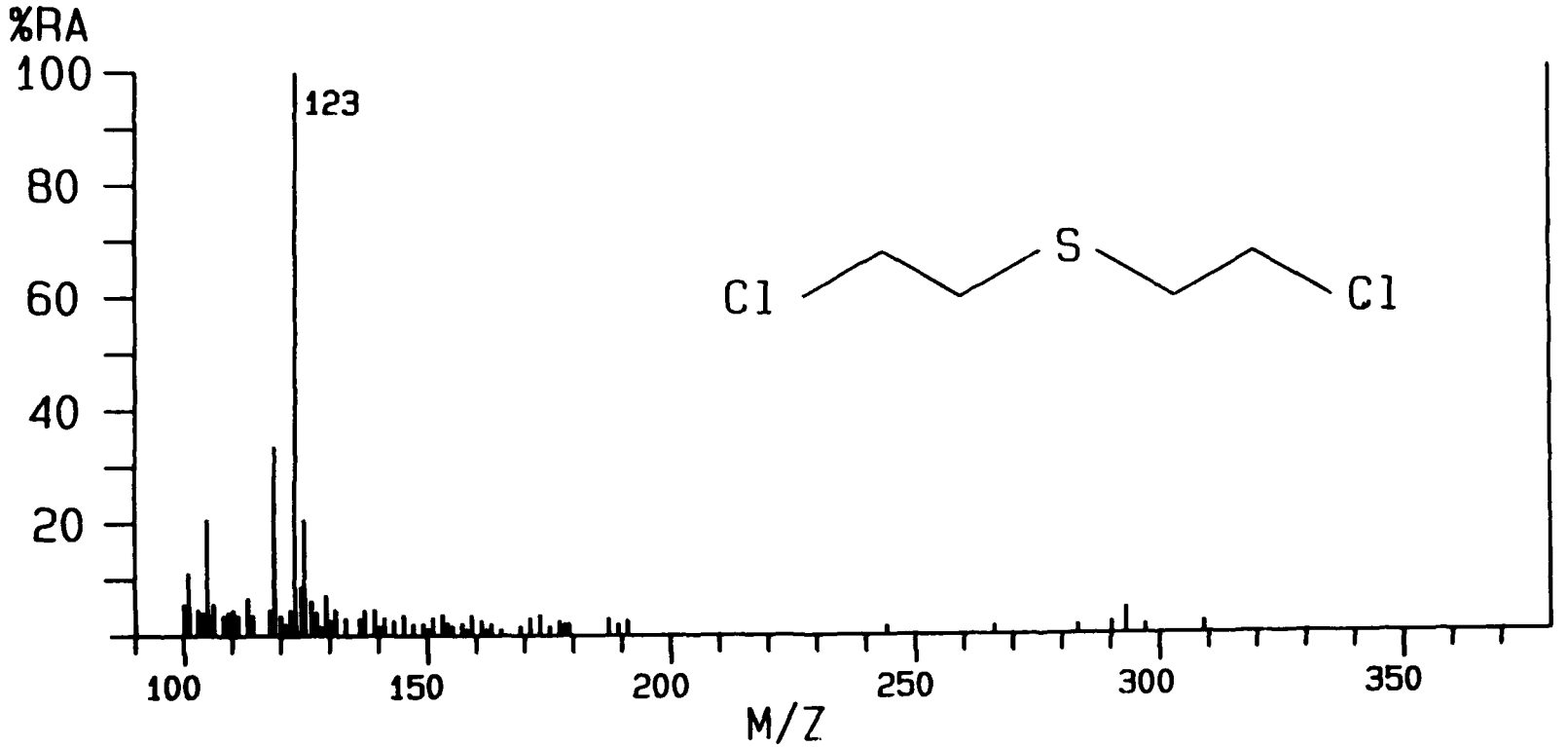


Figure 3. TSP Spectrum of Mustard (1) (mol. wt. = 158).

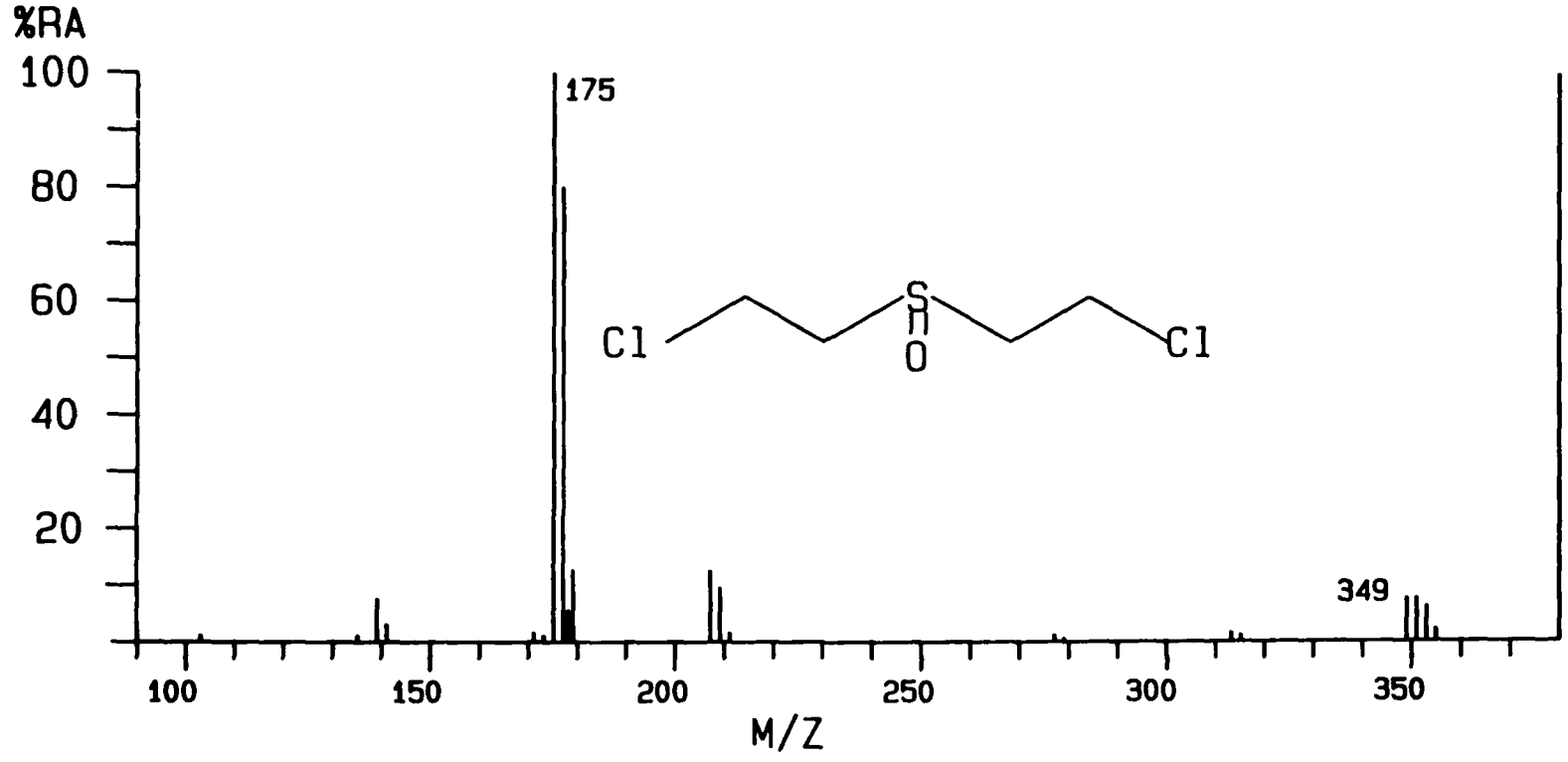


Figure 4. TSP Spectrum of Mustard Sulfoxide (5) (mol. wt. = 174).

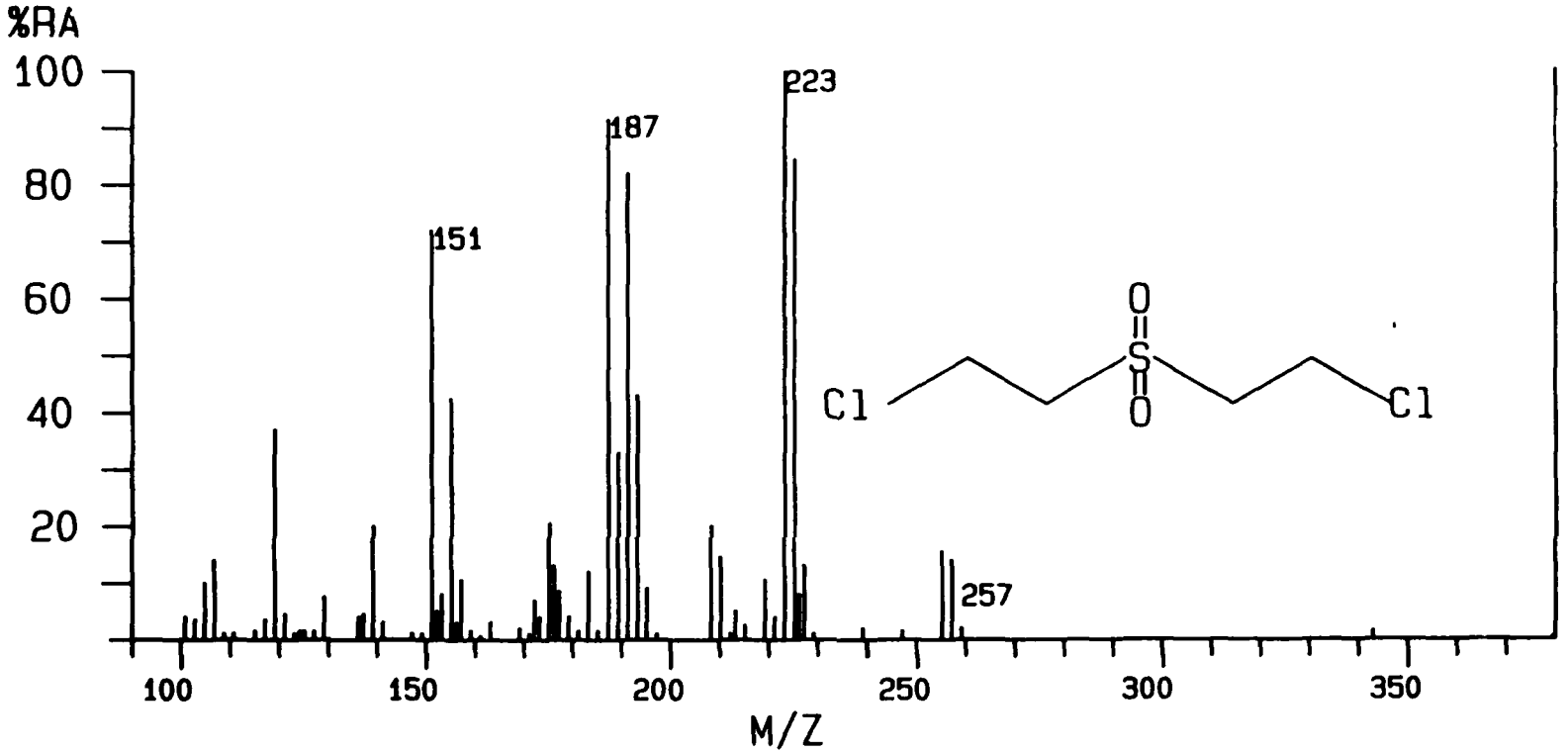


Figure 5. TSP Spectrum of Mustard Sulfone (6) (mol. wt. = 190).

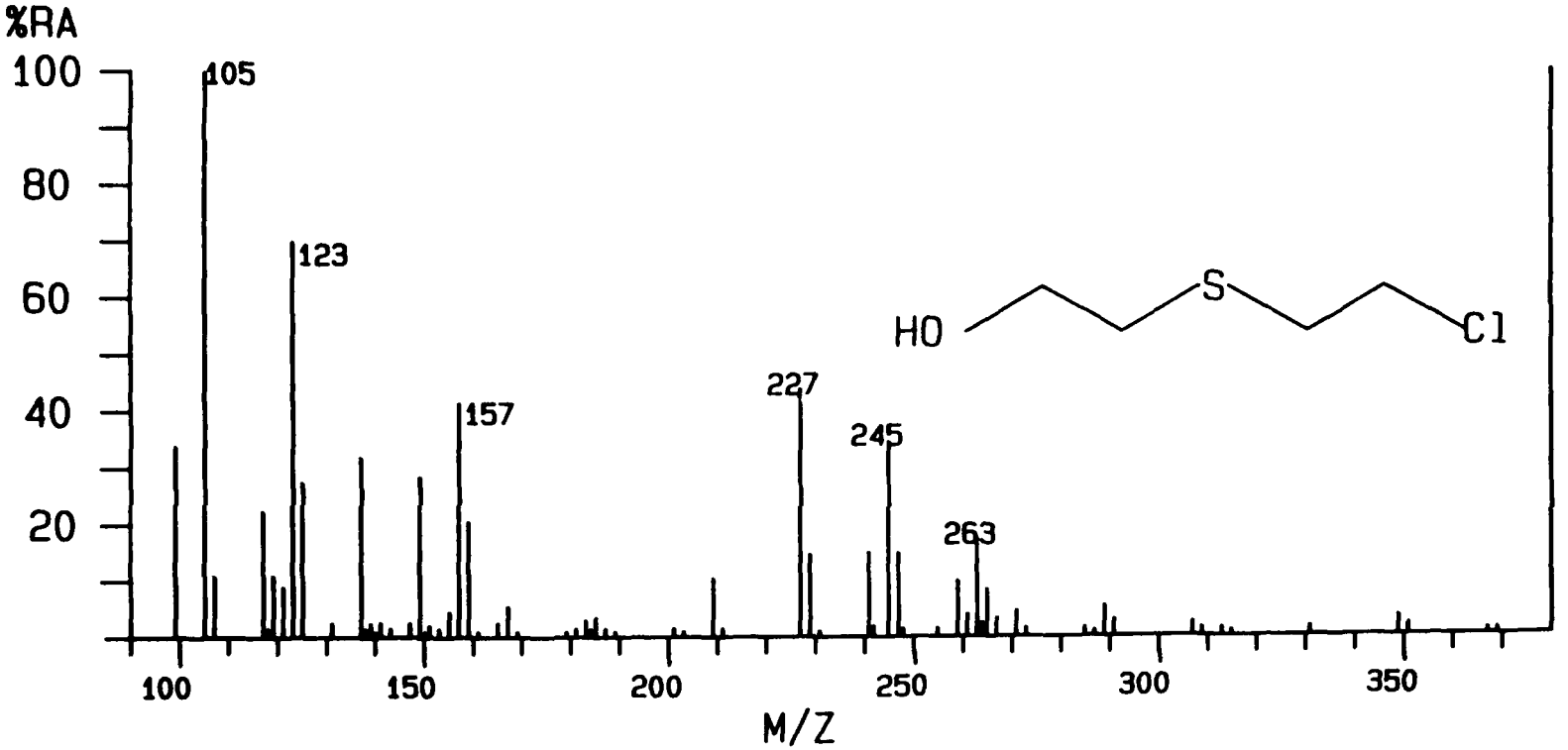


Figure 6. TSP Spectrum of Half-Mustard (3) (mol. wt. = 140).

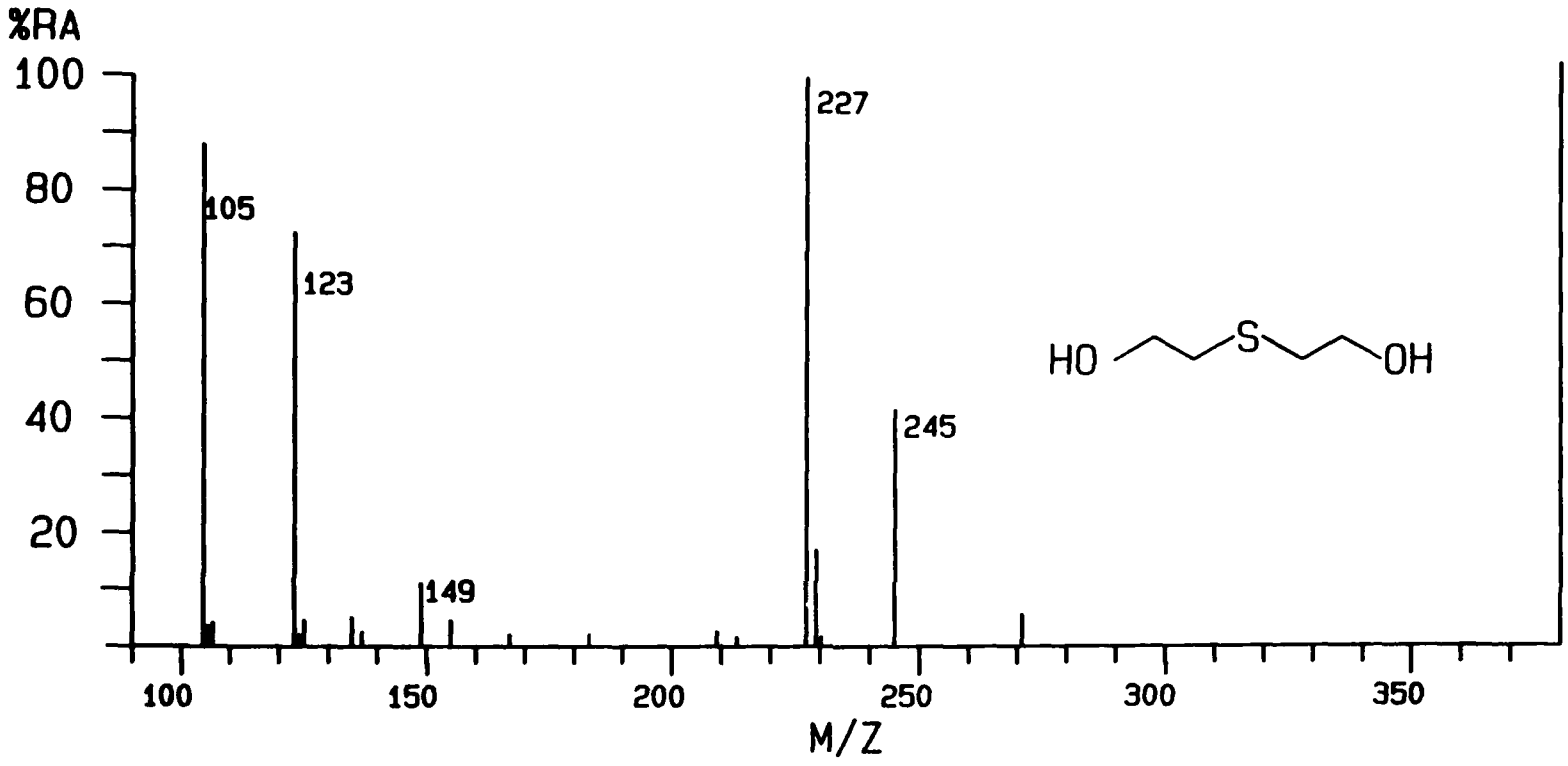


Figure 7. TSP Spectrum of Thiodiglycol (4) (mol. wt. = 122).

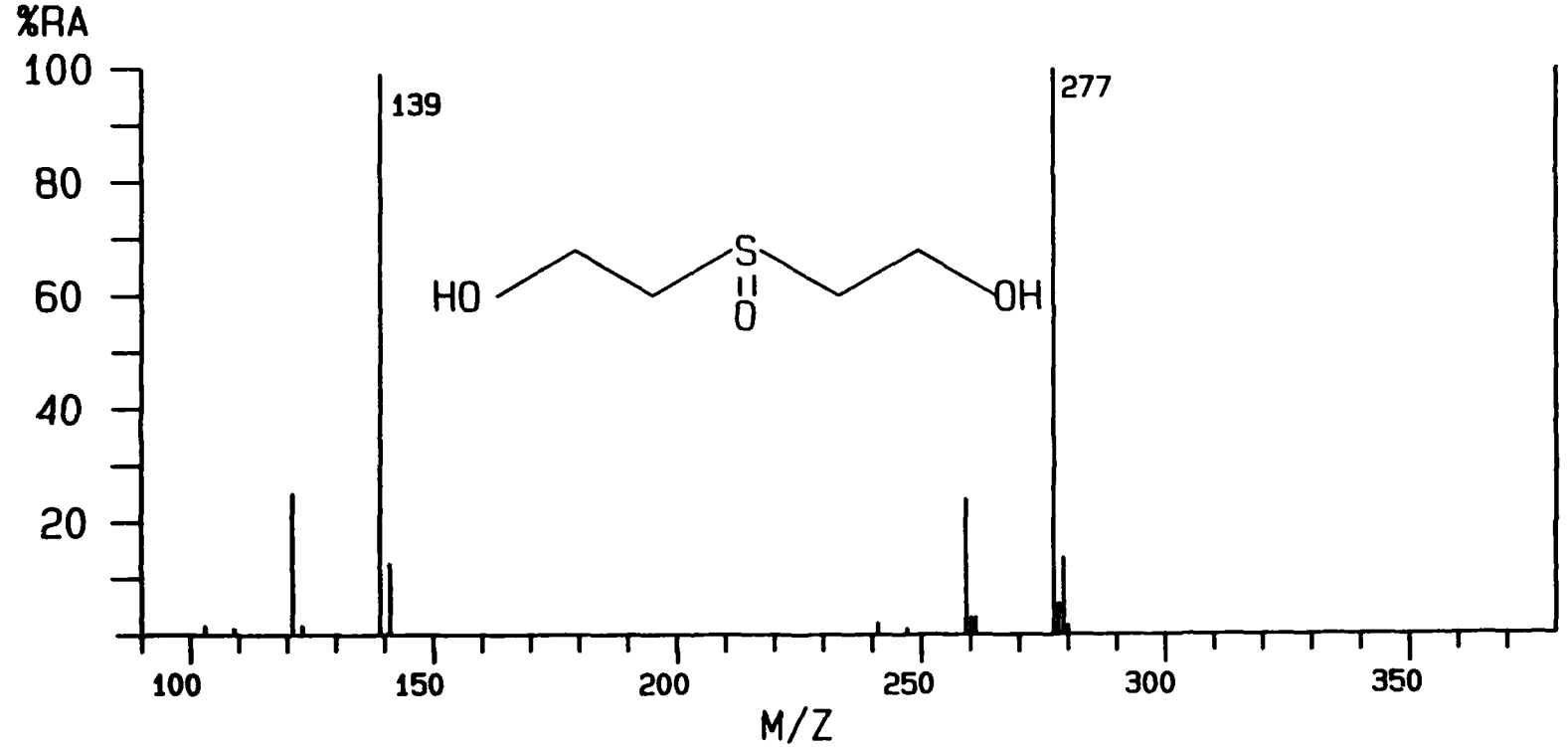


Figure 8. TSP Spectrum of Thiodiglycol Sulfoxide (7) (mol. wt. = 138).

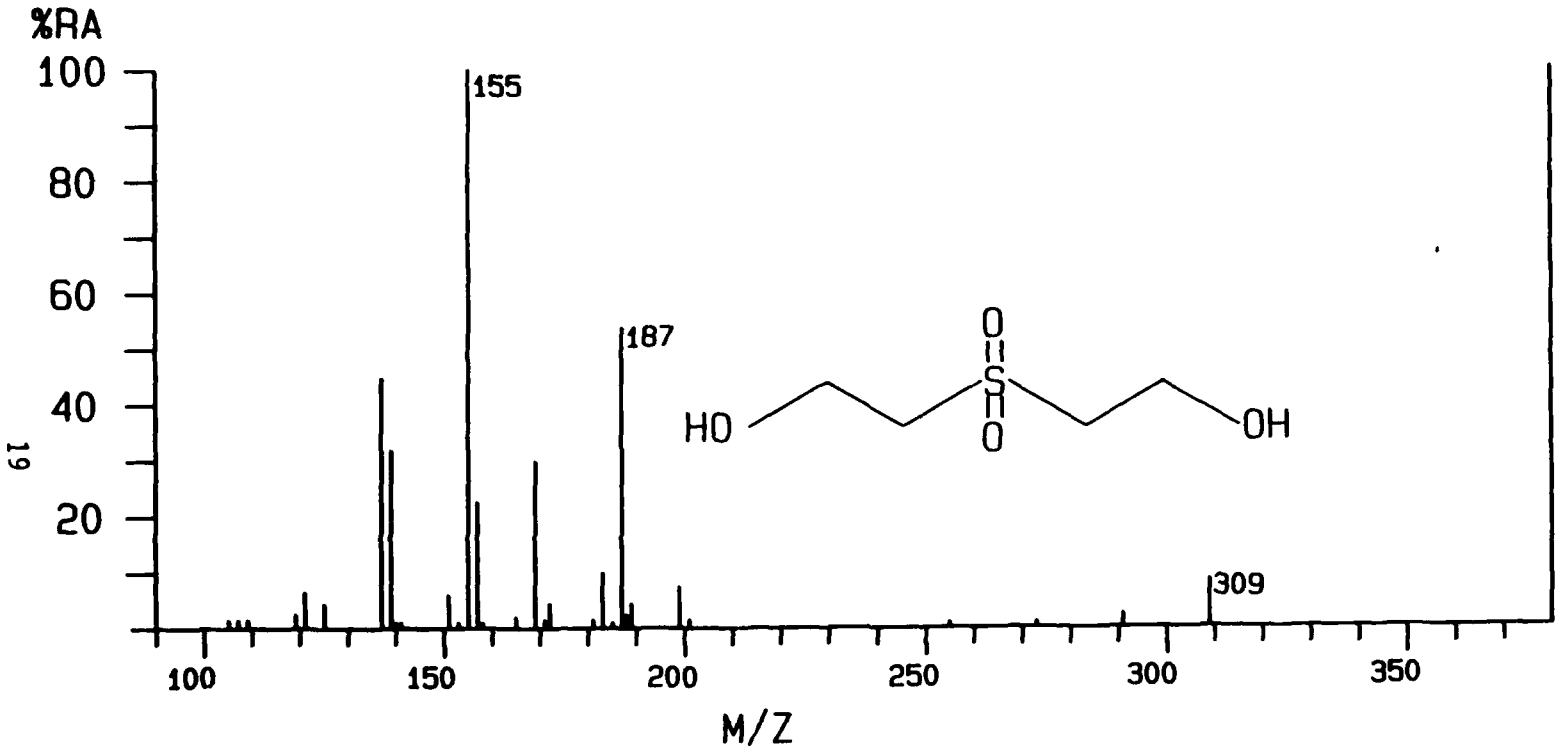


Figure 9. TSP Spectrum of Thiodiglycol Sulfone (8) (mol. wt. = 154).

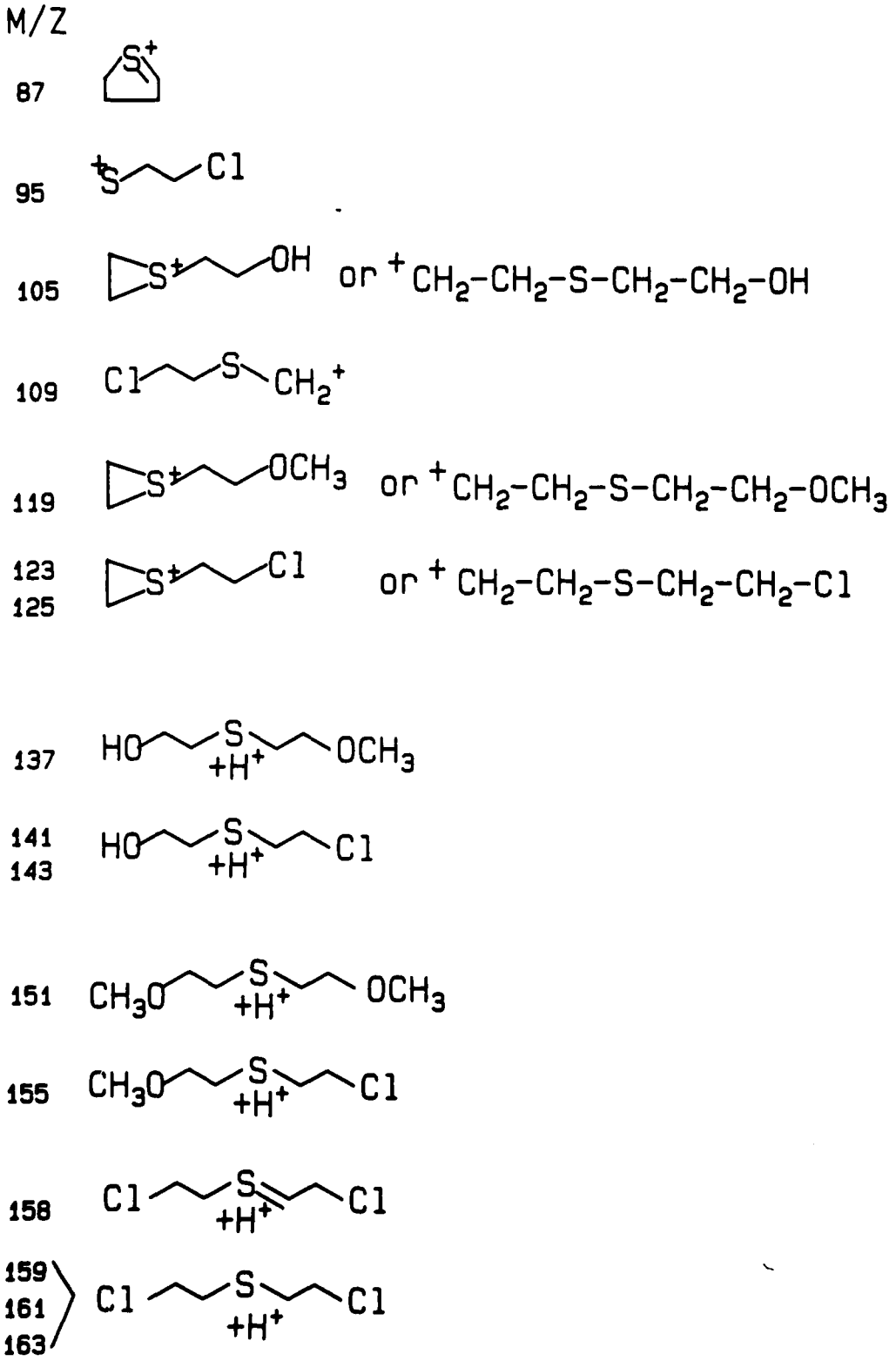


Figure 10. TSP Degradation Ions of Mustard.

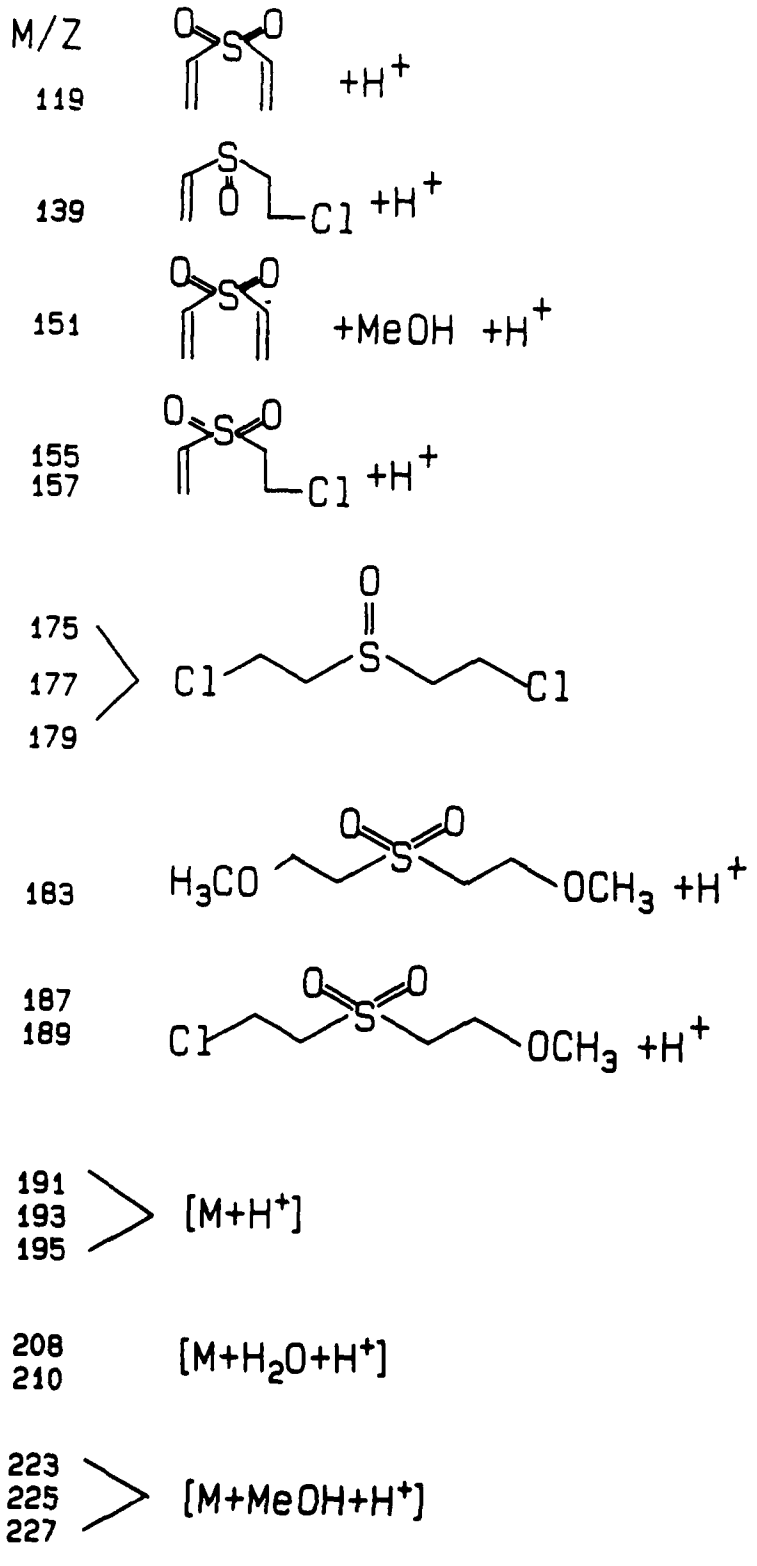


Figure 11. TSP Degradation Ions of Mustard Sulfone.

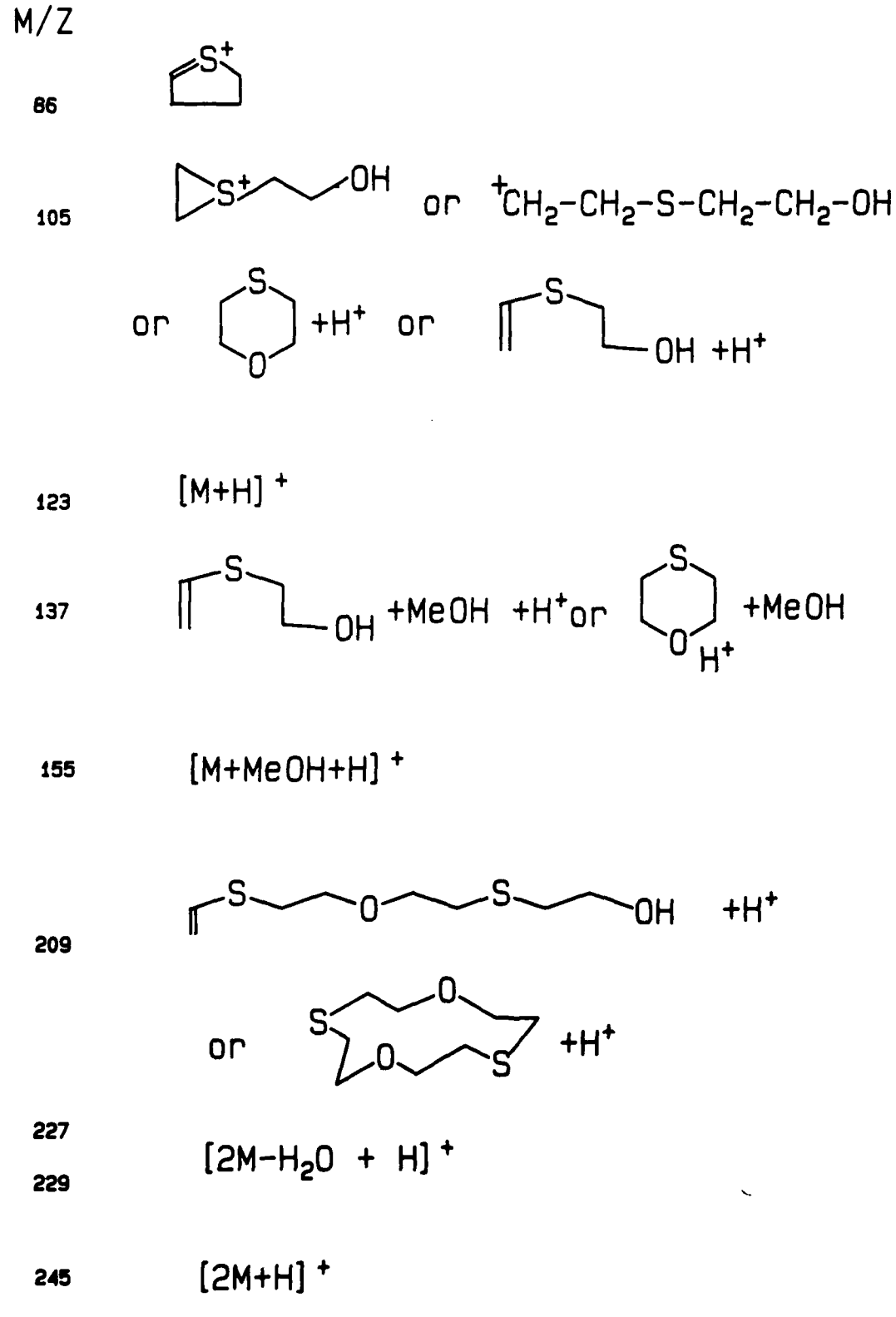
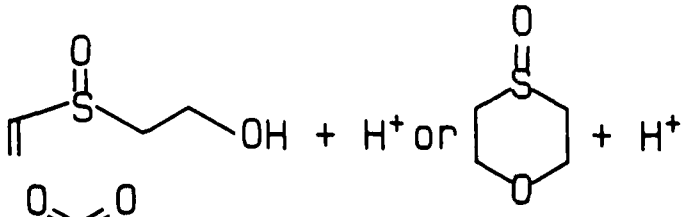
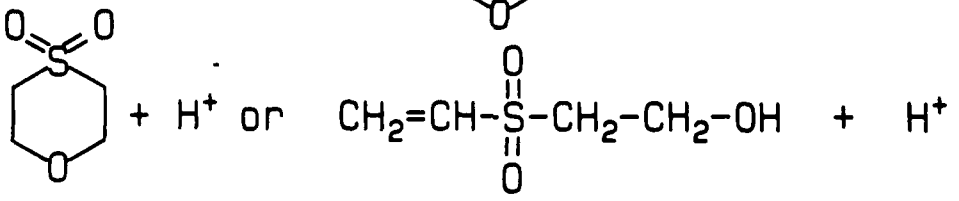
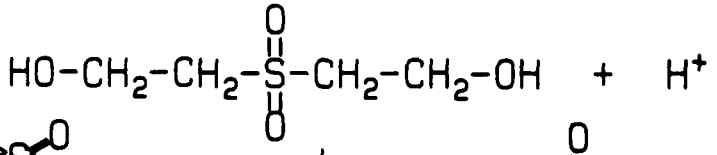


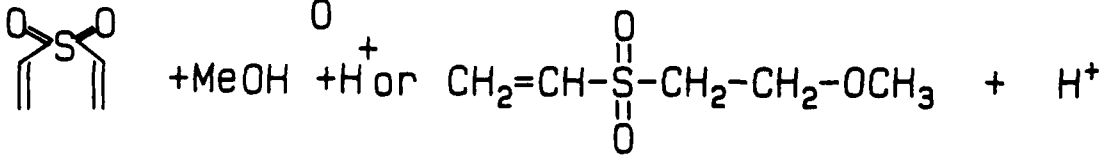
Figure 12. TSP Degradation Ions of Thiodiglycol.

M/Z

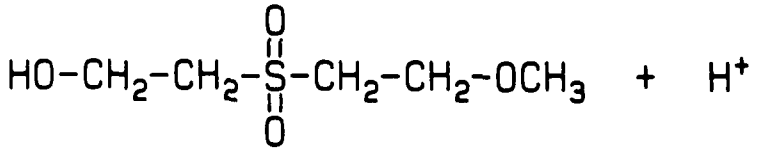
121 

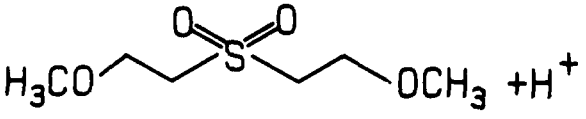
137 

139 

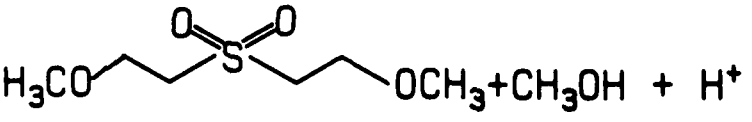
151 

155
157 $M+H^+$

169 

183 

187 $M + CH_3OH + H^+$

199 

309 $2M + H^+$

Figure 13. TSP Degradation Ions of Thiodiglycol Sulfone.

Direct injection TSP LC/MS of mustard and its metabolites yielded mass spectra dominated by a nucleophilic substitution reaction. Figures 3-9 represent the positive ion spectra. Possible structures for degradation ions of 1, 4, 6, and 8 are shown in Figures 10-13 (only partial spectra are given as illustrations). Ions representative of both condensed-phase reaction intermediates and products were observed in the TSP degradation of all analytes. The scheme illustrates the case in point for 1. Particularly interesting is the appearance of ions that would demonstrate the presence of the postulated three-membered, cyclic sulfonium ion intermediate (2) or its equivalent (Figures 10-13). Figure 4 describes the fragmentation pattern of mustard sulfoxide. Here again, one can see the presence of the cyclic sulfonium ion or its equivalent (m/z = 139). The presence of the ion m/z = 141, representing the 37Cl isotope is also noticeable with the most prominent ion being the $[M+H]^+$. The formation of thiiranium ions was seen for all analytes except mustard and thiodiglycol sulfones (6 and 8). These compounds lack the unshared pair of electrons needed to initiate the attack on the beta carbon to form 2 or its equivalent. The loss of chloride from 1 has been reported to occur readily to yield a highly reactive positively charged intermediate.[21] This intermediate reacted with water to produce 3 that goes on to react again with water to form 4. Thiodiglycol is stable at room temperature; under TSP conditions, the compound can form the thiiranium intermediate (Figure 12, m/z = 105). All of the analytes produced spectra showing the substitution of a methoxy group for either the terminal hydroxy or chloro groups. For example, the spectrum of 1 exhibited ions at m/z = 151, corresponding to the dimethoxy analog (Figure 10). Mass spectra of the chloro- and hydroxy-congeners differed qualitatively in the methanol matrix. One major difference was the tendency of the hydroxy-compounds to form dimers, trimers, and other polymers. For example, 4 exhibited an ion at m/z = 245 that represents the product of two molecules of the substrate. This ion had a relative abundance of 45% (Figure 7). The formation of protonated dimeric clusters under CI conditions or species produced by reacting with one or more molecules of the solvent such as $[M+H]^+$, $[M+NH_4]^+$, $M+2NH_4]^+$, and $[2M+NH_4]^+$ has been recently reported.[11,22,23] However, 1 did not produce a dimer under nonaqueous conditions. Polymer-formation appears to be a characteristic of the negative ion spectra of the thiodiglycol congeners (compare Figures 1 and 2).

Another important difference between chloro- and hydroxy-congeners is the appearance of the distinctive chlorine isotopic abundance patterns. For example, mustard has ions at m/z = 123 and 125. For mustard, the relative ratio between the m/z = 123 and 125 ions is approximately 4 to 1, which is quite different from that expected from the relative isotopic abundances of ^{35}Cl and ^{37}Cl (approximately 3 to 1). However, small amounts of water present in the solvent and sample may cause the formation of thiodiglycol from mustard, which may account for the aberrant isotopic ratio. Other ions indicative of the presence of water in the mustard samples are seen at m/z = 105, 137, 141, and 143 as shown in Figures 3 and 10. This observation indicates the importance of controlling analytical conditions with respect to the presence of nucleophiles. This possibility may permit the use of nucleophilic susceptibility in the analysis of mustard analogs by TSP LC/MS. One such method may be the addition of an alkylamine to derivatize the mustard in the TSP probe source and thus to produce in situ a derivative free of interferences. Another way to analyze mustard-like compounds is to use solvents of very low nucleophilicity to provide spectra indicative of only the analyte.

Variations in the ion currents of the protonated dimeric form of methanol versus a characteristic mustard ion is illustrated in Figure 14. Decreases in a solvent-related ion current with the introduction of mustard demonstrated the CI quality of the discharge TSP process. The abundance of the cyclic sulfonium ion or its equivalent (m/z = 105) does not mirror the fact that the solvent ion decreases as closely as the total ion current plot for mustard. This observation appears to be consistent with a breakdown reaction that is independent of reagent gas ions.

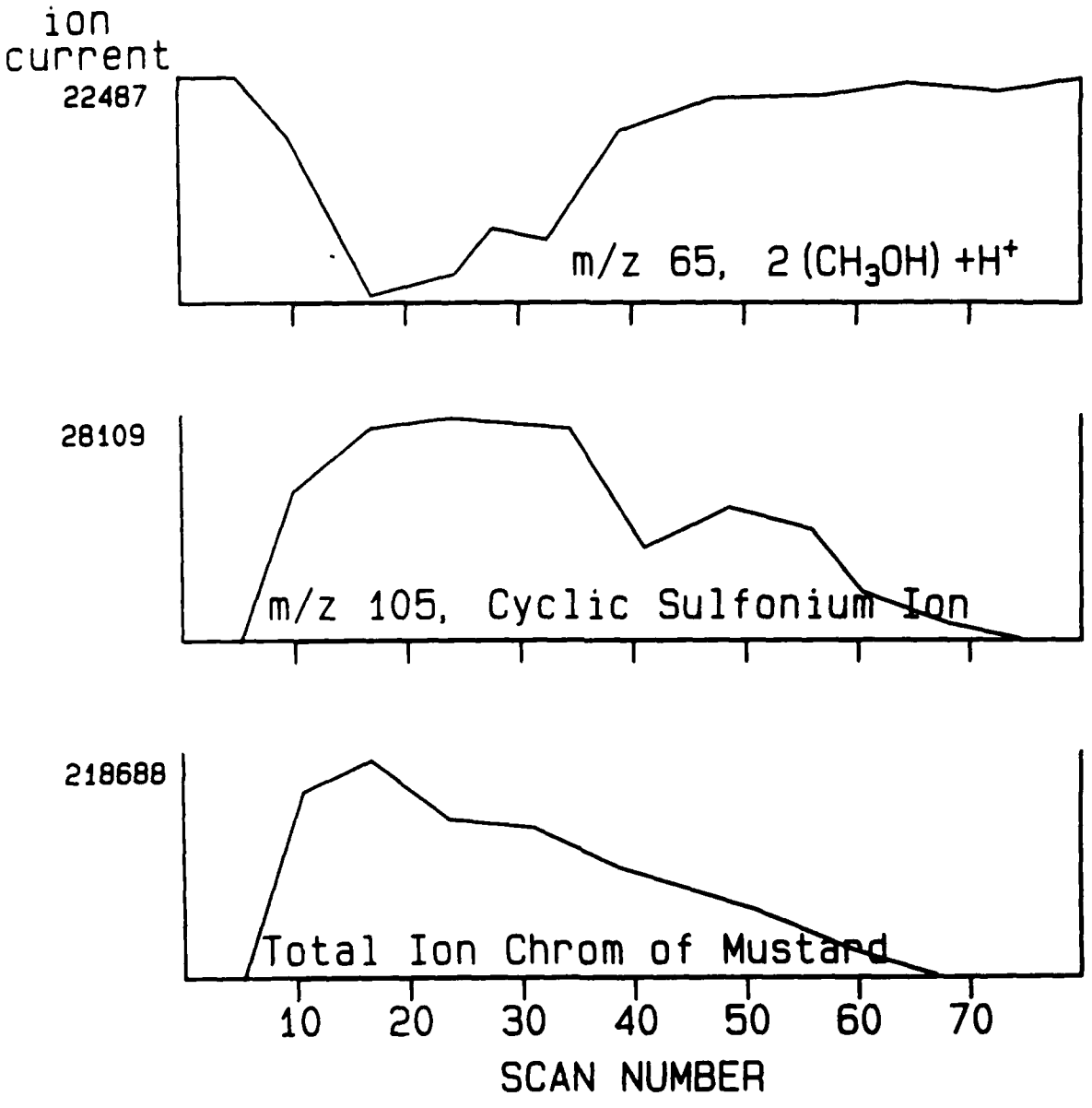


Figure 14. Reconstructed Ion Chromatograms of Solvent vs. Mustard Ions.

4. CONCLUSIONS

Some of these findings were discussed at a seminar in 1987 and at the Annual Conference held during the month of November 1987. Recently, we came across a paper describing the use of isobutane induced, CI capillary, GC/MS analysis of mustard and other sulfur-containing compounds.[24] The paper also cited that the $[M+H]^+$ ion formed the most prominent peak.

Recently, a semiquantitative, rapid, TLC method of analysis of mustard and its metabolites has been reported.[25] These workers reported that the reversed-phase TLC gave totally unsatisfactory results. Hence, this precluded the direct analysis of aqueous extracts by reversed-phase TLC. The TSP LC/MS analysis of mustard and its metabolites yielded structural information required to confirm the presence of mustard derivatives. The breakdown patterns and possible reactions of mustard and related analytes in the TSP are dominated by nucleophilic substitution. Of the breakdown ions observed, the cyclic sulfonium ions or their equivalents are the most significant. This normally unstable intermediate has not only been postulated as an intermediate in the hydrolysis of mustard but also has been implicated in many of the physiological and biological properties of mustard and its analogs. As seen by the presence of the thermally generated decomposition products, many of the observed fragment ions appear to be the protonated species. Because of the unusual reactivity of mustard, the $[M+H]^+$ peak could not be detected in its TSP LC/MS spectra. Indeed, this observation is in agreement with the recent observations of D'Agostino and Provost, who were unable to produce and detect $[M+H]^+$ or $[M+NH_4]^+$ ions during capillary column-induced CI .[23] However, it was interesting and rewarding to note that the most prominent ion in the case of mustard sulfoxide happened to be the $[M+H]^+$ ion.

The formation of the cyclic sulfonium ions or their equivalent species during the TSP analysis of these compounds is seen in cases that are expected to generate such species. Consequently, such species are not observed for mustard and thiodiglycol sulfones. Indeed, this is what it should be, for these sulfones lack the unshared pair of electrons required to form the cyclic species. Thus, the formation of the cyclic sulfonium species or their equivalents is observed during the TSP analysis of compounds having the ability to generate such species. The above contention is supported by the recent report claiming the involvement of the cyclic sulfonium species in the case of bis[(2-chloroethylthio)ethyl] ether and 1,14-dichloro-3,12,16-trithia-9-oxatetradecane.[24]

Although GC/MS is considered to be the method of choice for quantifying mustard, the TSP LC/MS technique provides useful supplementary information that is not possible to obtain otherwise. In addition, the TSP LC/MS has an added advantage over the GC/MS, in that aqueous extracts of the substrates can be directly analyzed by TSP LC/MS. Thus, the TSP environment can generate unique conditions useful in the analysis of reactive species.

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